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Instant insight: think outside the cell

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Abstract

Proteins perform many different functions critical for life, from building our muscle structure to digesting our food. These large biological molecules each have a unique three-dimensional shape which they require to perform their function. In protein deposition diseases (PDDs), however, a disease-specific protein molecule unfolds from its normal shape and assembles together with like molecules into insoluble rod-shaped fibrils. These protein deposits can be found in the brain, skeletal tissue and various organs; in some cases they may become large enough to disrupt tissue structure and function.

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Instant Insight: Think outside the cell

Proteins are large biological molecules which perform many different functions critical for life (e.g. making up the structure of muscle, digesting our food). They have a unique three-dimensional shape that is required for them to perform their function. In *protein deposition diseases* (PDDs) a disease-specific protein molecule unfolds from its normal shape and assembles together with many other unfolded molecules of the same protein to form insoluble rod-like fibrils. One of the most prevalent and costly PDDs is Alzheimer's disease (AD) but there are more than 40 diseases in this group including Parkinson's disease, mad cow disease and motor neurone disease. The protein deposits can be found in the brain, skeletal tissue and various organs; in some cases they may become large enough to disrupt tissue structure and function. When it is considered that cells and their surrounds (extracellular spaces) are densely packed with thousands of different proteins, and are exposed to many stresses capable of unfolding proteins, it seems miraculous that there are not more of these PDDs.

Inside cells (i.e. intracellularly) there is a large amount of energy invested into ensuring that proteins reach and maintain their normal (native) shape. This quality control machinery includes molecular chaperones, which bind to hydrophobic (water-hating) regions normally buried inside the native shape of a protein, and sophisticated degradation machinery such as the proteasome. There is little doubt that these intracellular mechanisms protect our bodies from PDDs which would otherwise produce harmful protein deposits inside cells. But what happens outside cells where many PDDs, including AD, produce insoluble deposits? The answer to this question is the focus of our review. Very little previous work has examined this question, being instead directed towards those now relatively well understood intracellular mechanisms.

Recently, it was discovered that a small group of human blood proteins possess the ability to "chaperone" misfolded proteins (i.e. keep them soluble and inhibit their clumping together). Each of these “extracellular chaperones” (ECs; clusterin, haptoglobin and α_2-macroglobulin) is bound by specific cell surface receptors that can internalise them and their ligands for subsequent degradation inside the cell. The ECs and their receptors may comprise the foundation of an extracellular system for quality control of protein folding. Such a system may be overwhelmed in extracellular PDDs such as AD. Consistent with the model proposed, it has been shown that in mouse brains the clearance of extracellular amyloid-β peptide (which forms the plaques in the brain in AD) is much faster when it is bound to clusterin and slower when α_2-macroglobulin or the α_2-macroglobulin receptor are inhibited. Studies of the system(s) sensing and controlling protein folding in extracellular spaces of the body are in their infancy but in time are likely to produce important insights into the mechanisms underpinning extracellular PDDs. This will provide new opportunities to develop therapeutic strategies for a range of diseases that will have an increasing impact on an ageing world population.